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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/974,186	11/18/97	BOYLE W	A-378D5

HM22/1103

U.S. PATENT DEPARTMENT/RBW
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EXAMINER	
CAMPELL, B	
ART UNIT	**PAPER NUMBER**
1632	12

DATE MAILED: 11/03/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
8/974,186	Boyle et al
Examiner	**Group Art Unit**
Campell	1632

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☑ Responsive to communication(s) filed on 9/16/99.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☑ Claim(s) 49-53 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 49-53 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☑ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

Continued Prosecution Application

The request filed on September 16, 1999 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/974,186 is acceptable and a CPA has been established. An action on the CPA follows.

Specification

The application still fails to comply with the requirements of 37 CFR 1.821 through 1.825. The response of January 25, 1999 refers to an amendment inserting sequence identifiers throughout the specification, but this additional amendment was not found attached to the response. Claims 52 and 53 also fail to comply with the sequence rules because they do not recite a SEQ ID No. Compliance with the sequence rules is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49-53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, as previously stated (paper 4, pp. 2-4; paper 8, p. 2).

The newly presented claims are drawn to methods of "regulating the levels of osteoprotegerin in an animal," whereas the previous claims were drawn to a method for treating bone loss. Before it can be determined whether the specification is enabling, the Examiner must construe the claims to determine what is being claimed (MPEP 2164.04). The specification does not disclose any purpose for regulating osteoprotegerin (OPG) levels other than treatment. Therefore the claims are still construed as treatment methods, and remain rejected for the reasons set forth previously.

Furthermore, the claims now also encompass methods for decreasing OPG levels, e.g. by antisense therapy. Determining which particular oligo sequences will be effective as antisense reagents is an unpredictable art. The accessibility of a target sequence depends on RNA secondary structure, which can not be accurately modelled (Milligan et al., p. 1924, last paragraph). Milligan et al. also teach that an oligo's specificity for the target sequence increases with length, but begins to decrease again beyond a certain length (p. 1926, col. 1). Thus it is not clear that oligos of 6 or 50 bases would be effective. Adding a few nucleotides to an effective sequence can abolish its activity. For example, Westermann et al. found that adding 4 or 7 bases to either end of an effective oligo sequence eliminated antisense activity (Fig. 1 and Table 1, compare oligos B and C with oligo A). Hoke et al. found that shifting the oligo target sequence by one or two bases reduced antisense activity by a factor of three, and shifting the target sequence four bases in the opposite direction completely abolished antisense activity (cols. 15-17). Hoke et al. conclude that "there are no rational explanations or rules that would predict active sequences" (col. 16, lines 52-53), and that "there are no obvious regions of a target mRNA that can be predicted to be effective targets for antisense oligonucleotide induced down regulation of protein synthesis" (col. 17, lines 7-10). Bennett teaches that inhibiting expression of a gene product is not as simple as "designing a single oligonucleotide to hybridize to a target gene, ordering the oligonucleotide from the DNA synthesis lab, and adding it to cells." Rather, "proper use of antisense oligonucleotides is a highly demanding and rigorous scientific challenge." "Identification of active antisense oligonucleotides requires screening multiple oligonucleotides designed to hybridize to different regions on the target mRNA to identify optimal target sites on the mRNA" (all quotations p. 434, cols. 2-3).

Several problems have been encountered when attempting to use antisense oligos (known to be effective *in vitro*) in humans, including stability of the oligo and lack of targeting to the desired cell type. Stein et al. teach that those skilled in the art do not yet accept the premise that oligos effective in preclinical experiments will necessarily prove to be effective therapeutic agents (p. 1011, last paragraph). Wagner states that while oligos "show great promise", development of delivery systems is essential. Wagner

concludes that "critical evaluation of antisense [oligos] *in vivo*...should eventually lead to the development of improved methods in antisense therapy for human diseases" (p. 335, last paragraph, emphasis added). Stull et al. state that "[n]ucleic acid drugs must overcome several formidable obstacles before they can be widely applied as therapeutics" (p. 476). Stull et al. highlight the problems of delivery to the correct cell type, uptake by the target cell and correct subcellular localization of oligos, concluding that "the delivery and entry of nucleic acid drugs into the target site remains a major obstacle to the successful introduction of this aspect of the molecular biology revolution into a clinical setting" (pp. 476-478). Wu-Pong states that "[a]lthough [oligonucleotide] analogues demonstrate activity in certain cell and cell-free systems, many problems must be solved before they can be effectively used in vivo" and that "to fully realize the potential of [oligonucleotide] technology, pharmaceutical innovations will be necessary in many areas" (pp. 108 and 110, respectively). Miller et al. state that "an adequate *in vivo* delivery system remains a fundamental problem in the practical application of antisense therapeutics" (p. 92). Rojanasakul reviews current methods for targeting and delivery of antisense oligos and concludes that "development of the antisense concept is still faced with several obstacles" (p. 126). Taken together, these references clearly show that those skilled in the art still do not regard the path from *in vitro* activity to practical therapeutic application as straightforward or routine.

The specification provides no guidance regarding what portions of the OPG mRNA are effective target sequences, nor is there any guidance regarding how antisense oligos should be administered and what conditions can be treated by such administration.

For the reasons set forth above and in previous Office actions, it would require undue experimentation to use the claimed methods. This is particularly true given the nature of the invention, the breadth of the claims, the absence of specific guidance and working examples, the quantity of experimentation necessary and the unpredictable nature of the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce Campell, whose telephone number is 703-308-4205. The examiner can normally be reached on Monday-Thursday from 8:00 to 4:30 (Eastern time). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on 703-308-2035. The FAX phone numbers for group 1600 are 703-308-4242 and 703-305-3014.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Bruce Campell

BRUCE R. CAMPELL
PRIMARY EXAMINER
GROUP 1600